MEDICAL STAFF CONFERENCE

Gonococcal Sepsis and Arthritis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. EDELMAN:* The topic for discussion today is gonococcal sepsis and arthritis. The case will be presented by Dr. Feldman.

DR. FELDMAN:† The patient, a 26-year-old white man, had been in his usual state of excellent health until three days before admission to hospital when generalized malaise, diffuse joint stiffness, and tenderness around the third right proximal interphalangeal joint developed. He noted prominent pain on motion of the knees, but said that these joints were neither red nor swollen. At the same time he felt feverish and had several shaking chills. The next day pustules appeared on the dorsum of his left hand, on the thigh, and later on the palmar aspects of the fingers and on the soles of his feet. The skin lesions began as small, red, tender spots which progressed to central pustule formation. He punctured one lesion, and purulent material exuded.

The patient had had numerous sexual contacts, the most recent one ten days before admission. He denied urinary symptoms or penile discharge, but an open sore near the penile corona had been healing poorly. There was no history of venereal disease. Although he denied regular use of drugs, he had given himself an intravenous injection of amphetamine ten days before admission.

On physical examination, the patient was alert and afebrile and the vital signs were within normal limits. Pertinent physical findings were confined to the skin, joints and genitalia. There were several tender red macules 5 to 10 mm in diameter with raised central pustules or necrotic centers on both hands, the left thigh and the left great toe. Periarticular tenderness was present around the third right proximal interphalangeal joint, but no other abnormalities were apparent. A partially healed ulcerative lesion was present near the penile corona, which was erythematous and tender. Purulent material could be expressed from the urethra. No cardiac murmurs or other stigmata of endocarditis were present. The abdomen was soft and there was no organomegaly or hepatic friction rub.

Leukocytes in peripheral blood numbered 7500 cells per cu mm with a normal differential count The hemoglobin was 14 gm per 100 ml. Urinalysis was within normal limits. Gram stains of smears prepared from the skin pustules revealed numerous polymorphonuclear leukocytes; no microorganisms were seen. Similar smears of the urethral exudate revealed polymorphonuclear leukocytes with Gram-negative and Gram-positive diplococci which were located predominantly outside the cells. Four blood cultures and cultures of the urethral exudate and urine sediment were negative for organisms. Darkfield examination of the penile lesion was not carried out. A VDRL test was negative. Routine blood chemical determinations, an x-ray film of the chest and an electrocardiogram were all within normal limits. Penicillin was administered intravenously for ten days and the patient had an uncomplicated recovery.

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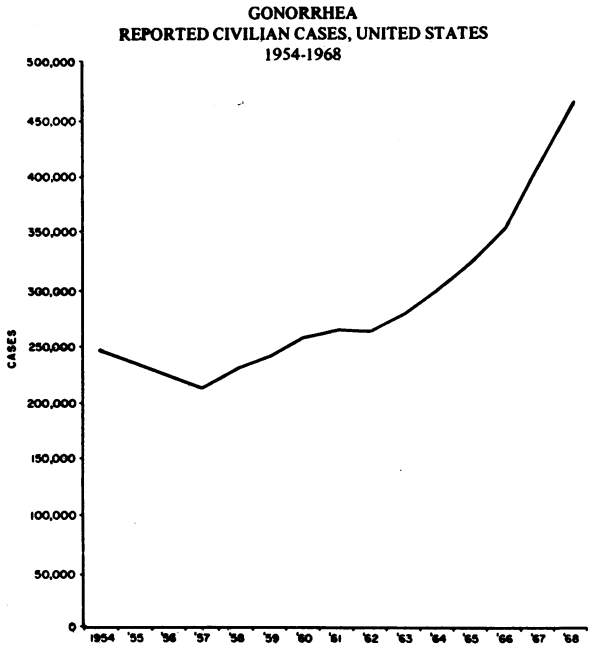

Chart 1.—Reported cases of gonorrhea in the civilian population between 1954 and 1968. (Reproduced by permission of the publisher.[3])

DR. EDELMAN: The case will be discussed by Dr. Drutz.

DR. DRUTZ:* The patient, a young man who experiments with drugs and is sexually promiscuous, is typical of many who are likely to have gonorrhea in our prevailing social climate. We did not isolate the gonococcus from this patient, but the clinical course was sufficiently distinctive to permit the diagnosis of gonococcal sepsis. Gonococcal organisms were recovered from two other patients recently admitted with gonococcal sepsis and arthritis.

Gonococcal sepsis and arthritis have been relatively infrequent problems since the inception of the antibiotic era. Yet these three patients were seen at Moffitt Hospital within a 14-day period. In this regard, it is well to bear in mind that this hospital is largely a diagnostic referral center. Dr. Austin Brewin of San Francisco General Hospital has informed me that three cases of gonococcal arthritis a month is not at all unusual at that institution. Thirty-six years ago, Myers and Keefer[1] pointed out that gonorrhea was one of the most common causes of acute and chronic arthritis. While we have not regained this pinnacle in 1970, we seem to be rapidly approaching it. As a recent editorial in the *Annals of Internal Medicine* indicated, "by any standards, gonorrhea is out of control in the United States."[2]

*David J. Drutz, M.D., Assistant Professor of Medicine.

The Resurgence of Gonorrhea

Shown in Chart 1 are the reported cases of gonorrhea in the civilian population between 1954 and 1968.[3] In this 15-year period, the number of cases doubled. However, a survey of private physicians published in 1963 revealed that 70 percent of gonococcal infections are treated outside of public clinics and that only 10 percent of these are ever reported.[4] Thus, the true incidence of gonorrhea in the United States is unknown, but conservative estimates indicate that 1.7 million new cases occur in this country every year.[2] The reasons for the resurgence of gonorrhea are complex and closely interrelated.

Short Incubation Period. With an incubation period of only three to five days, gonorrhea becomes highly infectious almost immediately.

High Communicability. Virtually every intimate sexual contact involving a patient infected with gonorrhea places the infecting agent in an ideal site for multiplication in the new host, namely a mucosal surface.

Asymptomatic Carrier. The carrier state is an extremely important mechanism by which gonorrhea is perpetuated in a population. Women are a particular problem in this regard because they may have neither urethritis nor even a vaginal discharge, and therefore may unknowingly harbor and transmit the gonococcus. Indeed, direct swabs from normal-appearing, but infected, cervixes can transmit gonorrhea to male volunteers.[5] Asymptomatic gonococcal carriage in males has been far less frequent and symptoms of urethritis generally prompt medical consultation. However, a few cases have been documented,[6] and asymptomatic gonococcal infection in the rectum of male homosexuals is an increasingly important source of dissemination of the microorganism.[2]

Absence of Immunity. Gonorrhea is not an infection which confers significant immunity upon its victims, and therefore repeated infections are common.

Changing Sexual Mores. There has been a change in sexual attitudes in the Western world with the advent of birth control pills and a generally more permissive moral climate. This change is reflected in the high incidence of gonorrhea in teenagers.[7] Yet, if sexual permissiveness were the

major reason for the upsurge of gonorrhea, there should have been an equivalent rise in primary and secondary syphilis.[2] This has not been the case. Again the aspect of communicability arises, for whereas a large proportion of patients with syphilis are asymptomatic, most are non-infectious. By contrast, even the asymptomatic carriers of the gonococcus are highly infectious.

Inadequate Identification of Contacts. It became apparent as early as 1947 that the reduction in syphilis morbidity in response to penicillin was proportionately much greater than the reduction of morbidity in gonorrhea. Efforts to deal with gonorrhea were reinforced, and in 1952 a system known as "speed zone epidemiology" was introduced. With this technique, male patients were interviewed, and every effort was made to examine and treat their contacts within 72 hours. In 1956 "antibiotic quarantine" was added. Here, contacts were treated with benzathine penicillin G to maintain prolonged blood levels in an attempt to prevent reinfection for two to six weeks.[7] Unfortunately, as we shall see, the low blood levels of penicillin produced by regimens of this type may tend to select out relatively penicillin-resistant gonococcal strains.

Despite enthusiastic application of these techniques, the incidence of gonorrhea was not significantly reduced. Cases simply cannot be found and treated as fast as they occur. A further obstruction to case finding is the absence of a practical diagnostic serological test for gonorrhea.

Decreasing Penicillin Sensitivity of the Gonococcus. There has been a progressive decrease in the susceptibility of the gonococcus to penicillin.[8] This is particularly apparent in Southeast Asia, where prostitutes have been shown to harbor gonococcal strains which are relatively resistant to penicillin. However, the same trends have been observed in the United States, particularly on the West Coast. A contributing factor to the problem in the Orient may be the relative ease with which antibiotics are obtained. Indeed, prostitutes often treat themselves continuously with low doses of antibiotics as prophylaxis against venereal infection. Under these conditions, drug use only assures the selective acquisition of gonococcal strains that are more resistant to penicillin.

In order to understand precisely what is meant by a resistant gonococcus, it should be appreciated that group A beta-hemolytic streptococci are generally sensitive to 0.02 mcg per ml of penicillin, pneumococci to 0.04 mcg per ml, and non-penicillinase-producing staphylococci to 0.4 mcg per ml. From 1945 to 1954, most gonococci were sensitive to 0.03 mcg per ml of penicillin. In 1955 nearly one-fourth of strains required 0.06 to 0.12 mcg per ml for inhibition. By 1964 strains were requiring up to 0.6 mcg per ml, and in 1969 some gonococcal isolates required up to 2.0 mcg per ml of penicillin for inhibition although most strains were still sensitive to 0.3 mcg per ml.[7,9]

It should be emphasized that the penicillin resistance to the gonococcus is purely relative and does not indicate that this antibiotic is no longer useful in treating gonorrhea. What it does indicate is that the favored single-shot outpatient treatment for gonorrhea may no longer be practical as larger and larger doses of penicillin are required to achieve therapeutic levels in the body.[8]

The Local Manifestations of Gonorrhea

Depending largely upon the sexual proclivities of the patient, gonococci may be introduced into the body in a variety of sites. The distinct propensity of the gonococcus to invade mucosal surfaces and the general resistance of squamous epithelium to infection account for the usual symptoms of gonorrhea. In males, symptoms of urethritis with burning on urination and penile discharge are the usual initial manifestations of infection. Urethritis may develop in females also, but they more frequently harbor the gonococcus asymptomatically or have varying degrees of vaginal discharge. In patients who engage in anal intercourse, proctitis may be the presenting problem.[9] It is likely, however, that gonococcal proctitis is often asymptomatic. Patients engaging in oral-genital relationships may present with pharyngitis of some severity.[10,11] It is clear that gonorrhea must at least be considered in the differential diagnosis of any sore throat, and that Gram-negative diplococci in the pharynx cannot be dismissed as Neisseria catarrhalis, or indeed Neisseria meningitidis, without appropriate bacterial culture data. Conjunctivitis is a well-known manifestation of ophthalmia neonatorum, developing when a newborn infant has passed through a gonococcus-infected birth canal. It is not generally appreciated that the anogenital orifices may also be infected by the same mechanism, and that infants may go on to have gonococcal sepsis and arthritis.[12]

Progressive Infection

In males who do not seek medical attention, the initial acute anterior urethritis spreads to involve the posterior urethra, resulting in frequency and urgency of urination, and terminal hematuria. Columnar epithelium lining the urethral glands, prostatic ducts, prostate, seminal vesicles, vas deferens, and epididymis (as well as the anterior urethra) is especially vulnerable to invasion by the gonococcus. As infection spreads posteriorly, perineal discomfort occurs. There may be acute urinary retention as the prostate and seminal vesicles are invaded, and acute seminal vesiculitis may be complicated by high fever and pain in the suprapubic, inguinal and sacral areas. With invasion of the epididymis, testicular swelling and pain develop. In the absence of treatment, there is a tendency to chronicity with progressive tissue destruction. This is the situation which predisposes to formation of urethral strictures.

In females there may be remarkably few symptoms so long as the infection is localized to the lower genitourinary tract. The spread of gonococci from the cervix to the fallopian tubes, however, is generally accompanied by severe lower abdominal pain and pelvic peritonitis. It is this sequence of events which is termed acute pelvic inflammatory disease (PID). Repeated bouts of infection may result in marked tissue destruction with formation of abscesses, tubal strictures, and ultimate loss of fertility. Chronic PID may be a source of considerable pain and disability.

Extragenital Manifestations

The extragenital manifestations of gonorrhea are the result of gonococcal bacteremia and reflect the affinity which the gonococcus appears to hold for serosal and synovial surfaces. The exact incidence of bacteremia in patients infected with the gonococcus is unknown, but appears to be quite low. Even patients with clear evidence of bacteremic disease, such as skin lesions or arthritis, may have only a 15 percent chance of having a positive blood culture.[13]

It is essential to appreciate that gonococcal bacteremia and its complications may occur in the presence or absence of overt genital infection. In females sepsis may evolve from an asymptomatic carrier state following menstruation, pregnancy or unusual sexual stimulation.

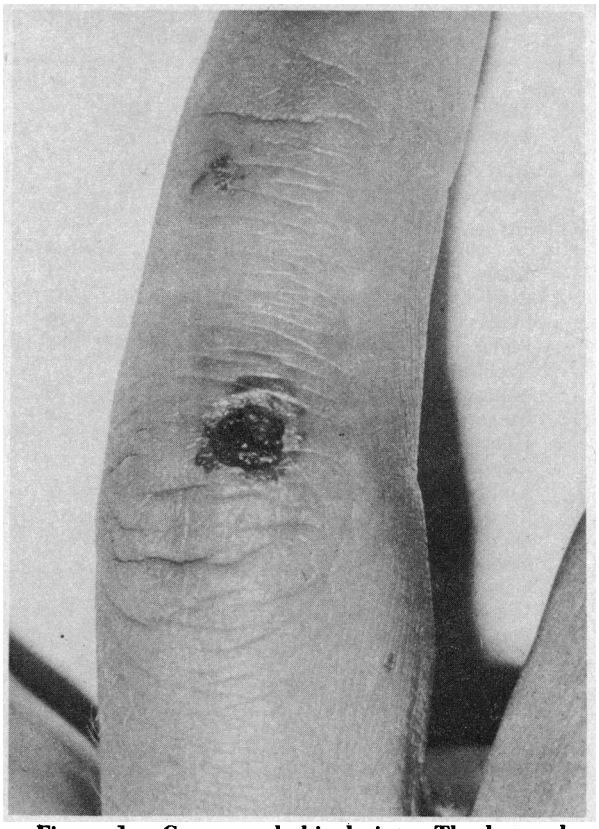

Figure 1.—Gonococcal skin lesions. The larger lesion is a characteristic hemorrhagic papule. Overlying the distal interphalangeal joint is an erythematous macule containing a central pustule which has ruptured.

It has followed vigorous prostatic massage in males. Further, gonococcal sepsis has been documented following prostatectomy or hysterosalpingectomy in elderly patients in whom gonococci have apparently been dormant for years.[14,15]

Skin lesions and arthritis are the most common extragenital manifestations of gonococcal septicemia; however, several other manifestations will also be discussed.

Skin Lesions. Gonococcal skin lesions are usually widely distributed, sparse (seldom more than a dozen), and tend to occur on the distal portion of the extremities, especially around joints.[16] The initial lesion is a pinpoint erythematous macule (Figure 1) which rapidly evolves into one of three characteristic patterns:[17,18]

- Vesicles or pustules located centrally on a broad erythematous base
- Hemorrhagic papules (Figure 1)
- Hemorrhagic bullae

The lesions are typically tender and reveal the

TABLE 1.—*Summary of Clinical Features in 140 Cases of Gonococcal Arthritis

1. Sex			
Males		104	
Females		36	
2. Polyarthritis		107	
Monarthritis		33	
3. Joints Involved			Tenosynovitis
Knees		127	4
Ankles		56	32
Wrists		44	19
Metacarpophalangeal		27	6
Shoulders		25	
Metatarsal and laryngeal		27	6
Fingers		31	4
Hips		23	
Elbows		20	
Lumbar part of spine		14	
Toes		19	
Sacro-iliac		8	
Heels		7	
Cervical part of spine		6	
Dorsal part of spine		4	
Sternoclavicular		3	
Costosternal		2	
Temporomandibular		3	
Olecranon bursa		1	
Acromioclavicular		1	
4. Associated Features			
Conjunctivitis		21	
Abscess of tendon sheath		2	
Death		7	
Endocarditis	2		
Glomerulonephritis	1		
Intercurrent pneumonia	3		
Progressive gonococcal infection	1		
Iridocyclitis		4	
Glomerulonephritis		2	
Pregnancy		4	
Bacteremia		5	
Recovered	3		
Died	2		
Endocarditis		2	
Keratodermia blennorrhagicum		4	
Sterile meningitis		1	

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presence of vasculitis histologically. Gonococci can rarely be cultured from these lesions. A paper by Ackerman and associates[17] contains especially good color photographs of typical gonococcal skin lesions. In the absence of therapy there is a small, but distinct, propensity for gonococcal skin lesions to recur in crops. Indeed, there may be a striking similarity to chronic meningococcemia in this regard.[17] However, the combination of focal hemorrhagic and vesiculopustular lesions in a patient with fever and arthritis is highly suggestive of gonococcemia.

Arthritis. Arthritis is perhaps the most widely appreciated extragenital manifestation of gonorrhea. It has been emphasized that the clinical presentation of gonococcal arthritis has changed in recent years. "What was once a relatively common complication of genital gonorrhea that predominantly affected males and left a large proportion of patients with residual joint disability now seems to be a relatively uncommon disease occurring principally in females and responding dramatically to penicillin with no residual joint damage."[19] The change has likely been wrought by the advent of effective antibiotic therapy. When urethritis develops in males they usually seek early medical attention, and the disease is aborted before systemic infection can develop. On the other hand, females with asymptomatic genital infections often do not see a physician until systemic manifestations of gonorrhea have developed. The arthritis is, however, very responsive to treatment with penicillin.

Although the severest arthritic manifestations of gonorrhea may be localized to one or two joints, gonococcal arthritis at its inception is characterized by polyarthralgias or frank polyarthritis. These findings suggest that multiple joints are initially infected but in only a few does progressive disease develop. Alternatively, it has been suggested that the polyarthritis is a hypersensitivity phenomenon to products of the gonococcus.

Table 1 summarizes the clinical features of 140 cases of gonococcal arthritis seen by Keefer and Spink[20] at the Boston City Hospital before the beginning of the antibiotic era. It is apparent that virtually any joint in the body may be involved, but the knees, ankles, and wrists most commonly. An extremely important clue to gonococcal arthritis is the presence of tenosynovitis around the wrists, ankles, metacarpophalyngeal joints, and knees. The associated tenderness is so great that the patient may not voluntarily move the joint or allow it to be touched. Occasionally, tendon sheaths may be involved without associated arthritis. Presumably the gonococcus invades the tendon sheaths; abscesses have been observed in these sheaths.

Synovial fluid examination generally reveals polymorphonuclear leukocytosis. It has been said that white cell counts greater than 30,000 cells per cu mm are usually associated with positive joint fluid cultures, while counts below this value

occur with sterile fluid.[21] There are, however, exceptions to this general rule. Even in the best of circumstances (joint fluid dripped directly on a chocolate agar plate and immediately placed in a CO_2 atmosphere) only 25 percent of joints reveal the gonococcus.[13,20]

There appears to be a distinct relationship between the duration of arthritis and the ability to recover the gonococcus from joint fluid. The result is that two syndromes of gonococcal arthritis can be recognized. In the first, arthritis occurs in a setting of acute illness and is accompanied by chills, fever and skin lesions. Joint effusion is not pronounced and synovial fluid cultures are usually negative, while blood cultures are more frequently positive. In the second form of gonococcal arthritis, bacteremia is asymptomatic, skin lesions are absent, and blood cultures are seldom positive. Joint effusion may be pronounced, and synovial fluid cultures are more likely to be positive. The explanation for this difference is presumably that patients symptomatic from gonococcal bacteremia seek medical care relatively early, before joint disease is well established. In contrast, patients with asymptomatic bacteremia usually do not consult a physician until they have persistent arthritic symptoms and for that reason are more likely to have positive joint fluid culture, more time having passed for bacterial multiplication.[19]

Conjunctivitis and Iridocyclitis. It is not generally appreciated that gonococcal sepsis may be accompanied by conjunctivitis or frank iridocyclitis. Keefer and Spink[20] reported that "metastatic catarrhal conjunctivitis," characteristically culture-negative, occurred in 10 to 20 percent of their patients with gonococcal arthritis. It appeared to be more commonly associated with negative than positive joint fluid cultures.

Endocarditis. Gonococcal endocarditis is no longer common, but it received a great deal of attention in the literature of the preantibiotic era. Unlike patients with other gonococcemia-related syndromes, those with endocarditis may be extremely ill with fulminating sepsis.[22] One characteristic by which gonococcal endocarditis might be suspected is the presence of two fever spikes a day—the so-called double quotidian temperature curve.

Meningitis. As of 1963, 26 cases of gonococcal meningitis had been reported in the medical literature.[23] It is possible that this diagnosis is missed when Gram-negative diplococci seen in the cerebrospinal fluid are automatically assumed to be Neisseria meningitidis.

Perihepatitis (FitzHugh-Curtis syndrome). Gonococcal perihepatitis has been classically considered a rare complication of gonococcal infection in females wherein microorganisms spread directly from the pelvis over the peritoneal surface of the liver. Symptoms include right upper quadrant abdominal pain, pleuritic in character and often referred to the shoulder, as well as tenderness, guarding, and a friction rub over the liver. The latter is not always present, but may be of great diagnostic value.[24] As symptoms of genitourinary gonorrhea may be minimal or absent, operation for acute cholecystitis may be needlessly performed. The "violin string" adhesions between the anterior abdominal wall and the liver which have been found in patients with known gonococcal pelvic infection are a reflection of this process. Recently the FitzHugh-Curtis syndrome was recognized for the first time in a male.[25] In this patient the gonococcus was isolated from histologically normal-appearing liver tissue. This perihepatic infection may have resulted from either bacteremia or from retroperitoneal lymphatic spread from the patient's genital gonorrhea.

Other Sites. Although rare today, a wide variety of metastatic complications of gonococcal infection have been reported, including liver abscesses, myositis, osteomyelitis, chondritis, pericarditis, myelitis, pleurisy, and pneumonia.

Diagnosis

The diagnosis of gonococcal sepsis rests in large part upon recognition of the clinical syndromes with which extragenital disease is associated, since culture of the gonococci from blood, skin or joints may be quite difficult. Demonstration of gonococci in genital tissues provides valuable supportive evidence for a diagnosis of gonococcal sepsis. In males with urethritis, the presence in urethral discharge of Gram-negative, kidney bean-shaped diplococci within polymorphonuclear leukocytes provides presumptive evidence for the diagnosis.[9] When the microorganisms are numerous, cultures will usually be positive. A negative smear does not mean that urethritis is non-gonococcal in origin, and cultures may on occasion grow gonococci.

Swabs of the anal canal in homosexuals or of the female genitalia will generally yield a variety of microorganisms in large numbers, obscuring the gonococcus even if present. Furthermore, asymptomatic carriers of the microorganism may have very few gonococci demonstrable. Finally, smears may be falsely positive for gonococci. In this regard, Garson and Thayer[9] found saprophytic Neisseria in 3.4 percent of women not infected with Neisseria gonorrhoeae.[9] In these circumstances, culture of the anal canal in the male and female, and culture of the female genitalia are required. Culture of the cervical os will probably detect about 82 percent of infected women.[9] However, up to 7 percent may harbor the gonococcus in the posterior vaginal fornix,[26] and up to 10 percent only in the rectum.[8] Therefore, culturing of the female with suspected gonorrhea can be considered to be complete only when material from the cervical os, the posterior vaginal fornix and the anus have been cultured. Urethral cultures appear to be relatively unproductive in females.[27] On occasion, culture of the spun urine sediment for gonococci may disclose the microorganisms in men or women.

The development of the highly selective Thayer-Martin[28] medium has assisted in the isolation of gonococci from specimens contaminated with a variety of microorganisms. This medium incorporates vancomycin, colistin, and neomycin which effectively inhibit the growth of nearly all microorganisms except oxidase-positive Neisseria gonorrhoeae and Neisseria meningitidis. It is currently believed that the growth of typical Gram-negative, oxidase-positive diplococci on Thayer-Martin medium suffices for the identification of the gonococcus. Carbohydrate fermentation reactions are reserved for positive identification of isolates from blood, conjunctivae, or synovial fluid or in instances where medico-legal considerations may occur.[9]

Other diagnostic aids for gonorrhea are also in use.[9] A fluorescent antibody test has been developed for detecting gonococci on direct smears of suspected positive exudates. A delayed fluorescent antibody test has also been utilized to examine material cultured for gonococci after a period of growth under carbon dioxide. Staining with fluorescent-tagged antigonococcal serum provides rapid identification of the microorganism and shortens the usual period required for conducting sugar fermentation reactions.

The current status of serological testing for gonorrhea has been reviewed recently.[29] The search continues for an adequate serological test. The literature of the 1930's and 1940's placed considerable emphasis on a gonococcal complement fixation test which was in common use at that time.[1,15] It is now appreciated that this test is not specific and that titers remain elevated for long periods of time after infection.

Treatment

Penicillin is the treatment of choice for gonorrhea and its extragenital manifestations. A daily dose of 5 to 10 million units of aqueous penicillin administered intravenously at intervals or by continuous infusion for a total of 10 to 14 days should suffice to treat gonococcal arthritis. Because penicillin crosses the inflamed synovial membrane quite efficiently, there is no need for intra-articular administration of the drug.[30] Indeed, penicillin is irritating to the joint space when introduced in this manner and may induce a chemical synovitis. The response of gonococcal arthritis to penicillin is generally so dramatic that it has been considered a diagnostically useful test.[21] The response is not always so rapid, however, and it has been emphasized that joint effusion may remain for some time after completion of therapy.[21] However, there is no question that penicillin has prevented the profound joint destruction and crippling which characterized gonococcal arthritis before the antibiotic era.

For patients with gonococcal sepsis who are allergic to penicillin, useful alternatives include cephalosporin derivatives (although a certain proportion of penicillin-allergic patients will also be sensitive to these drugs), tetracycline, or erythromycin.

DR. EDELMAN: Has anyone looked into the possibility that the birth control steroids might in some way alter the immunological response to the gonococcus?

DR. DRUTZ: I am not aware of any studies which have indicated that birth control pills have altered gonorrhea, except perhaps by lowering inhibitions toward sexual intercourse.

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DETECTING AIRWAY OBSTRUCTION

"Spirometry is the most common and the easiest means of detecting airway obstruction in a patient you suspect has one of the obstructive airway diseases. But I offer two warnings about its use: first, make certain that you have an abnormality, in the form of slowing of air flow on exhalation, which is irreversible. In other words, be sure that it does not respond to a bronchodilator significantly. Second, one examination, one spirometric determination, is not adequate for making the proper diagnosis. One should have this repeated because the next examination occasionally shows that the patient does not have airway obstruction at all."

—HAROLD A. LYONS, M.D., Brooklyn

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